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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/456,693	Applicant(s) LIPOVSEK, DASA
	Examiner Holly Schnizer	Art Unit 1653

FILE COPY

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *23-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *6* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in Paper No. 5 is acknowledged. In the Restriction of Paper No. 4, Claims 1-22, 28, and 31-35 were part of Group I. However, Applicants have indicated that Claims 28 and 31-35 were intended to be method claims and should be part of Group II (see Interview Summary of Paper No. 6). Thus, Group I, Claims 1-22 will be examined.

Status of the Claims

2. Claims 1-52 are pending, Claims 23-52 are withdrawn from further consideration as being drawn to a non-elected invention, and Claims 1-22 will be examined in this Office Action.

Drawings

3. The drawings filed 12/9/99 are objected to for reasons cited on the Form PTO 948.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1-22 are unclear as to what sequences are considered randomized since the claims do not contain a template sequence with which to compare. The specification defines randomized as "including one or more amino acid alterations relative to a template sequence (see p. 8). Many proteins contain fibronectin type III domains and the amino acid sequences of these domains vary even within one species. Thus, for example, one might view tenascin (comprising a type III domain) as a protein within the metes and bounds of the claims because it contains loops having amino acid alterations (randomized) as compared to a particular fibronectin sequence. On the other hand, another might view tenascin outside the metes and bounds of the claims because as compared to its own fibronectin type III domain, there are no amino acid alterations (no randomized loop). Addition of a template sequence with which to determine if a loop was randomized would clarify this matter.

7. The term "randomized" in Claims 1-22 is also unclear because the term generally refers to libraries of proteins. For example, Koide et al. (J. Mol. Biol. (1998) 284: 1141-1151; referenced in IDS of Paper No. 3) states that they prepared a library of FN3 in which residues in two loops were randomized (see abstract). One of skill in the art would understand this statement to mean that individual proteins in the library contained unique sequences relative to the other proteins of the library. Thus, the loop contains random sequences across the library. The confusion caused by this inconsistency is

further illustrated in the enablement rejection below. It appears that applicant may have intended to claim a library of proteins.

8. Claims 1-22 are indefinite as to the meaning of "corresponding" naturally-occurring fibronectin. As indicated on p. 13 of the specification, type III fibronectin domains occur in 2% of proteins many of which are not fibronectin proteins (e.g. tenascin). Thus, if a type III domain from a protein other than fibronectin is used, it is unclear as to what naturally-occurring fibronectin would be considered "corresponding".

Claim Rejections - 35 USC § 112

9. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. Applicant is referred to the interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 4, pp. 1099-1111 (available at www.uspto.gov) and the Examiner training Materials on Written Description also available at www.uspto.gov.

11. The claimed genus includes any protein comprising a fibronectin type III domain having at least one randomized loop, said protein being characterized by its ability to bind a compound that is not bound by the corresponding naturally-occurring fibronectin. The specification defines "randomized" as including one or more amino acid alterations

relative to a template sequence (see p. 8). Therefore, there are no limitations on how many amino acid residues can be substituted, inserted, or deleted and there are no limitations on what amino acid positions can be modified.

12. The Guidelines for Examination of Patent Applications under the Written Description Requirement states that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics (i.e., structure or other physical and/or chemical properties) by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Thus, when there is substantial variation within the genus (as in the present case), one must describe a sufficient variety of species to reflect that variation. In the present case, the claims are broadly drawn so that they encompass almost any protein containing at least one loop and that binds any compound not bound by a "corresponding" fibronectin. Proteins encompassed by the claims may have any binding activity or enzymatic activity and almost any structure (in addition to the "at least one randomized loop"). Thus, there is infinite variation in the claimed genus. The specification does not contain any actual reduction to practice of an individual protein of the invention. The specification describes screening a library of proteins containing three randomized loops of the 10th module of a type III fibronectin domain for TNF-α binding activity. The specification indicates that a percentage of the proteins of the library bound TNF-α (see Figure 10)

but does not describe any individual protein that binds TNF-α by any identifying characteristics. The specification does not provide any guidance as to the structure (amino acid sequence) of a TNF-α binding protein because the specification does not provide its amino acid sequence or even what amino acid positions of the fibronectin type III domain were randomized in the protein library used to isolate the TNF-α binding protein. The specification does not provide any reduction to drawings of any proteins that would be encompassed by the claimed genus or any relevant, identifying characteristics. In fact, the proteins of the claimed genus include any structure or function of interest.

13. Structural features that could distinguish the proteins of the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the claimed genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific guidance (such as which amino acid positions are randomized and which are not and what compound the protein binds) not general guidance is what is needed. One of skill in the art would conclude that applicant was not in possession of the claimed genus because the specification fails to disclose any common attributes or characteristics that identify members of the genus, the genus is highly variant, and the specification provides only a single disclosed species and this species itself is not specifically described. Therefore, written description requirement for a claimed genus is not satisfied in the present case because the specification does not provide a sufficient description of a representative number of species.

14. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a library of proteins, does not reasonably provide enablement for an individual undefined variant protein of a fibronectin type III domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

15. The claims are drawn to a protein comprising a fibronectin type III domain having at least one randomized loop and characterized by its ability to bind a compound not bound by the naturally occurring fibronectin. Thus, the protein is a variant of the fibronectin type III domain that contains amino acid modifications in at least one loop therein and which binds almost any compound of choice.

16. One of skill in the art would not know how to use the claimed proteins. The specification asserts that the scaffolds of the present invention can be used to identify, select, and evolve novel binding proteins (p. 13, lines 15-18). However, it appears that this statement is directed to the use of protein libraries disclosed in the specification rather than any individual protein sequence. As stated above, it is unclear how an individual variant can have a randomized sequence and thus it is unclear how an individual protein variant could be used to evolve novel binding proteins. As evidenced in the art (see Koide et al., Boder et al., and Smith et al. references from IDS of Paper No. 3 for example), those of skill in the art recognize the use of protein libraries

(containing proteins with varying sequences) to identify, select, and evolve novel binding proteins rather than any individual proteins.

17. The specification describes the construction of three libraries of proteins containing the 10^{th} module of a fibronectin type III domain of undisclosed origin or sequence (p. 21). These libraries were combined and undefined amino acid residues from three loops were randomized (p. 26, lines 15-22). The specification indicates that the complexity of one loop alone (FG loop) was 10^{13} and that the additional randomized loops provided potential for complexity too large to be sampled in a laboratory (p. 26, lines 20-22). Each of the proteins in this library is encompassed within the broad scope of the present claims yet the specification is silent as to how to use any one of them. A large portion of the proteins of the protein library of the present invention will not bind TNF-α and the specification has not taught how these proteins of unknown structure and function could be used. In the case of the proteins that do bind TNF-α, the specification does not indicate that any individual protein that binds TNF-α has been isolated and even if it has, the specification does not provide any information regarding the TNF-α binding protein such as its structure, sequence, or binding specificity. While the specification discloses how to use a library of proteins in the process of screening for novel binding proteins, the specification does not disclose how to use any specific individual protein variant.

18. Moreover, it appears that there is an assertion that the proteins of the invention (and especially those of Claims 13-17 and 22) can be used therapeutically (see p. 17, lines 6-19 and p. 29). However, the specification is silent as to the identification of the

proteins and what diseases they might be used to treat. The fusion to a complement protein is to be used to target cells yet the specification does not provide any guidance as to what cells would be targeted. The fusion of the claimed protein to a toxin is to be used to destroy cells but the specification does not indicate what types of cells or tissues are to be destroyed and in what type of disease. Finally, the use of the fusion of the claimed protein to albumin is intended to increase its half-life in the bloodstream yet the specification is silent as to why the fusion protein would be administered to a body in the first place. Absent a disclosure an identifying characteristic and function of the claimed proteins and what diseases they might be used to treat, one of skill in the art would not know how to use the proteins of the present invention.

19. In addition, the specification has not taught how to make a protein wherein compound binding is mediated by one or three loops. Protein binding is dependent on structure. And, the state of the art is such that it is acknowledged that one cannot merely predict protein function (such as binding function) from amino acid sequence information. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation that they will provide a particular binding function is unpredictable. (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure, pp. 14-16). Thus, even using library screening techniques, one of skill in the art would not know

which loops and which amino acid positions within those loops should be randomized to achieve binding through a specific number of loops.

20. The present specification describes the construction of a library of proteins yet does not describe any of the individual proteins contained therein. This general and vague description of individual proteins only invites those skilled in the art to use the claimed proteins in experiments to find out whether any individual protein is functional and what function it does have. As stated in Brenner v. Manson, 148 USPQ 689, 696 (US SupCt, 1966):

> A patent is not a hunting license. It is not a reward for the search, but a compensation for its successful conclusion.

Due to the large quantity of experimentation necessary to generate the infinite number of proteins recited in the claims and determine their activity if any, the lack of direction/guidance presented in the specification regarding structure or function of the proteins, the absence of working examples directed to any individual protein encompassed by the claims, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of random mutations on function and binding of a protein, and the breadth of the claims which fail to recite any specific structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial

inventive contribution on the part of a practitioner which would involve the determination of the function of any individual proteins claimed. It is this additional characterization of the protein that is required in order to obtain the functional and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

Claim Rejections - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

22. Claims 1-4, 6, 9, 12, and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Koide et al. (J. Mol. Biol. (1998) 284: 1141-1151; referenced in IDS of Paper No. 3).

23. Koide et al. teach the preparation of a phage display library using the fibronectin type III domain (FN3) in which residues in two loops are randomized at particular positions (see abstract and p. 1143, Col. 2, last paragraph). The tenth module of the FN3 domain is used in the disclosed experiments (p. 1142, col. 1, beginning at line 9 from bottom). Koide et al. teach the selection of FN3 mutants with a binding affinity for ubiquitin, a compound not bound by naturally-occurring fibronectin (p. 1142, Col. 2, lines 10-18). It appears that the ubiquitin binding is mediated by two FN3 loops (p. 1144, Table 1 and p. 1146, Col. 2). The FN3 mutant also lacks disulfide bonds (p. 1142, Col.

1, 4th line from bottom) and the integrin-binding motif (RGD) (p. 1144, Table 1). The proteins disclosed in Koide et al. were part of a fusion protein (p. 1148, Col. 2, lines 4-7 of "Phage Display Construction"). Thus, it appears that Koide et al. meet the limitations of the claims.

24. Claims 1-4 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Campbell et al. (Structure, 15 May 1994, 2: 333-337; referenced in IDS of Paper No. 3).

25. Campbell et al. discuss proteins containing fibronectin type III modules. For example, figure 1 shows that proteins such as tenascin, neuroglian, growth hormone receptor, CD4, and CD2 all contain fibronectin type III domains. Campbell et al. indicate that the fibronectin domains of these proteins have a common molecular topology (p. 334, Col. 2, second paragraph) and that proteins such as tenascin have an integrin binding domain and are similar to the tenth module of the type III fibronectin domain which does not contain a disulfide bond(p. 335, fig. 3 and Col. 1, first paragraph). The specification defines "randomized" as including one or more amino acid alterations relative to a template sequence (p. 8, lines 4-5). Assuming that the tenth module of the human fibronectin type III domain is the template sequence, the sequences of the proteins (such as tenascin) disclosed in Campbell et al. would be considered to have randomized loops since the sequences of these proteins are not identical. Furthermore, tenascin binds a proteins not bound by fibronectin. Thus, the Campbell et al. reference is considered to meet the limitations of the claims.